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Our training program in breast cancer detection and treatment continues to provide an excellent opportunity to train research fellows who demonstrate an interest in pursuing clinical and technical work relating to breast cancer. Through the dual mentorship system that we have adopted, each of the four current trainees is assigned to both a clinical specialist and a theoretical or research specialist. These complementary yet distinct professional perspectives constitute an invaluable resource throughout the program. Trainees also attend related seminars and conferences as part of their training. Trainee research encompasses a broad range of theoretical disciplines — genetics, biochemistry, electrical engineering, computer science, physiology, and tumor biology — as well as clinical disciplines such as radiology, oncology, pathology, and radiation therapy.

The University of Pennsylvania has developed a broadly-based graduate study program designed to apply theory to clinical practice in developing technology and procedures for the detection and treatment of disease. Throughout this year our work focused primarily upon improving methods of detecting breast cancer through magnetic resonance imaging of tissue, with significant attention paid to the characteristics of the disease at various stages. We have also striven to build upon current general knowledge of the metabolic and genetic parameters of the disease.

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J. Leigh 8/29/97

PI - Signature Date

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INTRODUCTION

The training program in Breast Cancer Detection and Treatment continues to provide an excellent opportunity to train research specialists in techniques for clinical and technical work relating to breast cancer. This program has established solid, productive teaching relationships between highly skilled and experienced cancer specialists and qualified recipients of their expertise. It has also fostered the development of diagnostic and therapeutic technology and the examination of clinical issues concerning this widespread disease.

The dual mentorship system that is in place ensures that each of the four trainees currently in the program is assigned both a clinician and a basic scientist as his or her individual advisors. The trainees benefit enormously from this system, which provides them with two distinct and often complementary sources of insight into the progress of their work and training. Program participants are currently trained in clinical and theoretical procedures by which to detect breast cancer at early stages; they also familiarize themselves thoroughly with the current knowledge about the biology and pathology of the disease and modern therapeutic practice as part of their training. Through their clinical advisor, trainees have access to the resources necessary for clinical research, as well as to the advisor's considerable background in clinical practice and parameters. The extent to which the trainees immerse themselves in clinical research varies according to the area of specialty to which they have gravitated and in which they are being trained.

The training faculty have been selected to fill either the role of clinician or of theoretical scientist on the basis of their specialization. In our search for qualified advisor candidates, we have sought to exploit existing collaborations between clinic and laboratory in the field of breast cancer research, in an effort to provide an advisory structure conducive to the trainee's academic and professional development.

Our fundamental goal remains to develop new techniques by which to detect and to treat breast cancer, and to enhance those already existing with new knowledge and technological improvements. A significant step towards this end is naturally the thorough training of qualified specialists seeking to gain experience in the theoretical and clinical fundamentals of breast cancer research.

What follows is a brief outline of the available clinical and research techniques in which the four members of the program are being trained, supplemented by a description of the related research undertaken by the trainees in the course of this funding year. We also present the academic status and professional profile of each trainee, as well as a discussion of his or her relationship with both individual advisors and pertinent information about each. Finally, we list the events, activities, and expectations associated with the trainees' participation in the program.

BODY

Magnetic Resonance Imaging (MRI) has established itself on the forefront of medical technology as a non-invasive clinical procedure by which to obtain highly accurate metabolic and oncologic profiles of isolated tissues within the body. The research division of our laboratory dedicated to the use of MRI in the detection and treatment of breast cancer remains extraordinarily active. Significant progress has been made in four areas of MRI research and development: diagnosing cancer, evaluating the local extent of breast cancer, screening high risk populations, and honing techniques for MR-guided breast interventions.

We have also made important advances in developing techniques by which to differentiate between benign and malignant enhancing breast lesions using MRI. Such techniques would greatly improve the specificity of breast MRI techniques, given that only about 40% of breast lesions detectable by MRI constitute actual cancer. We will continue to study the kinetics of image contrast enhancement and combine this with our work on breast architectural features in order to provide an improved interpretation model for breast MRI. It is hoped that this work will eliminate the problem of detecting false positives using such a technique.

We are continuing to study the ability of MRI to determine the local extent of breast cancer. This information is essential to the planning of appropriate therapies (lumpectomy vs. quadrantectomy vs. mastectomy). To date we have accrued over 150 patients with known breast cancer. In one half of these cases, the MRI measurement of the primary tumor was greater than standard clinical procedures and mammography would indicate. These results suggest that MRI could determine the local extent of cancer within a breast and subsequently serve as a guide in therapy.

A collaborative project which has received particular attention in the scientific community is the development of a technique by which to obtain a series of breast images of enhanced contrast. This imaging "movie" allows us to monitor the flow of a tracer dye through a given tumor, and consequently may aid us in determining the status -- benign or malignant -- of that tumor both speedily and accurately.

In the past year we have initiated our high risk screening program. In this study, patients whose family history places them at an extremely high risk for breast cancer (30% or greater life time risk), are screened for breast cancer yearly with MRI. The MRI technique extends, in a novel fashion, our high resolution technique for imaging a single breast so that both breasts may be imaged simultaneously.

The program trainees receive comprehensive instruction in the technological principles and procedures fundamental to the research described above. In addition, the trainees are currently engaged in research projects applicable to the broader fields of oncology and pathology. These are introduced below.

Experimental Demonstration of Photon Diffusion Imaging and Diffusive Emission Tomography in Highly Scattering Systems Approximating Breast Tissue

Recently there has been considerable interest in the use of multiple scattered light in optical tomography, due in part to potential medical applications. While X-ray CT, MRI, and PET have proven to be clinically useful, each suffers from limitations that restrict its application to widespread screening for cancer in asymptomatic patients. Principal among these limitations are cost and the patient's repeated exposure to ionizing radiation. Optical and near-IR wavelengths, at relatively low intensity, present no such limitations. Spatial variation in the absorption and scattering properties of a given tissue reveal much about its metabolic state, vascularization and structure. In addition, mapping the distribution of flourescently tagged antibodies, in analogy to

PET's use of radionuclides, may provide a means of localizing subclinical tumors with great specificity.

One problem with image reconstruction is that of mapping heterogeneities in scattering (diffusion) and absorption coefficients, as well the distribution of fluorophores. We have sought experimental validation of the numerical and analytical solutions to this problem in highly scattering systems that approximate tissue. In this environment, photons migrate in a random walk, colliding numerous times along the path from source to detector. We can thus describe light transport with integral equations, since it here occurs by means of diffusing waves. These equations are solved either numerically or by direct inversion in order to reconstruct spatial fluctuations in the absorption and diffusion coefficients of objects embedded in scattering media. In a similar manner, we may determine spatial variations in fluorophore number densities of these objects as well.

Our earliest experiments were performed within the time domain using a method of single photon counting directly correlated to time. This technique requires the injection, via optical fibers, of a brief (50ps) pulse of coherent, near-IR light pulse into a large, highly scattering bath that contains the object to be imaged. The bath and phantom possess optical properties similar to those of normal and abnormal tissues, respectively. By means of another immersed optical fiber, we then collected the transmitted light and passed it on to a microchannel plate detector, where we recorded the distribution of photon arrival times. We took multiple measurements as a function of source/detector fiber position, and so obtained three-dimensional images representing perturbations in the system's absorption and diffusion coefficients.

Our more recent work has focused upon taking measurements within the frequency domain; such a restriction had the twofold benefit of lowering equipment costs while providing more in-depth information. We generated an amplitude modulated, near-IR light source, such as a light emitting diode, in a continuous wave mode. At the same time, we recorded the intensity and phase of the transmitted light, again as a function of the relative positions of the source and detector fiber. With the incorporation of a fluorescent probe into our phantom, we have successfully reconstructed not only the spatially dependent absorption and scattering properties of the object examined, but also the spatial distribution of its fluorophores. We propose the use of higher frequency source modulations, where the re-radiation of the diffusing wave no longer undergoes a short time delay with respect to the source's modulation period. This should enable us to reconstruct not only the spatial distribution of the fluorophore but also its position-dependent lifetimes. Our technique may prove an invaluable tool in both functional imaging and tumor staging, since most fluorophores are quite sensitive to the characteristics of their environment.

In summary, photon diffusing imaging and diffusive emission tomography show potential for widespread use as a cost-effective and safe means of detecting breast carcinomas at early stages in asymptomatic patients. Primary tumors measuring less than 1 cm in diameter represent the smallest palpable and have less than a 20 percent chance of leading to metastasis. They are easily seen in images of high resolution, such as the ones generated using a combination of these imaging modalities. The ability to detect tumors during this pre-clinical growth phase, which typically spans 5 to 10 years, could reduce patient mortality significantly. In order to validate these tomographic reconstruction techniques empirically, we foresee clinical, *in vivo* studies.

Spin-Lattice Relaxation in Rotating Frame

Spin-lattice relaxation in the rotating frame, T1r, is characterized by a B1 field dependence rather than B0. As a result, low frequency motions — such as the thermal movements of macromolecules, diffusion, and exchange processes — have been suggested as the principle components in the mechanism of T1r relaxation. It is important to gain insight into such mechanisms, due to recent data which suggest that the use of T1r-weighted MRI can improve the detection of pathological developments in human breast tissue. Although previous studies have reported T1r dispersion curves for a variety of tissues, there has not yet been a thorough analysis of the specific mechanisms involved. Towards this end, we evaluated the changes in T1r dispersion in a variety of protein solutions and tissues under different solvent conditions; with this data in hand, we determined the relative importances of macromolecular structure and chemical exchange in T1r relaxation. Our study will serve to elucidate why T1r-weighted images normal and abnormal breast tissues demonstrate superior contrast and are easily differentiated. In addition, it is a significant first step in investigating the physical and biochemical properties of breast tissue that lead to observable differences in the T1r of normal and abnormal tissues.

Researchers have long held that the relaxation of protons in the component water of biological tissue, including breast tissue, is dominated by the interaction of such protons with macromolecules. This interaction may provide a useful tool in characterizing biological tissues as normal or pathologically altered. However, current understanding of the mechanism by which the nuclei of macromolecules and water protons are coupled is incomplete. Since the mechanism of relaxation at low frequencies is characterized by T1r dispersion curves, T1r analysis may be especially sensitive to the slow movements of macromolecules. The relaxation of water in bulk typically occurs by two means: the physical exchange of hydrogen atoms and/or spin transfer via cross-relaxation between macromolecular dipoles and water dipoles. Such relaxation may be affected by these slow macromolecular motions as well. Therefore, we analyzed the dispersion of T1r in mixtures of lyophilized algae — with and without deuteron substitution— in order to characterize the relaxation of water protons and DMSO protons. Our results indicate that hydrogen atoms covalently bonded to proteins are not a determinant in the dispersion of spin-lattice relaxation in tissue.

It has been noted that the processes by which the relaxation of water is stimulated in low static fields are distinct from those that stimulate relaxation in higher fields. One would not thus expect that, in biological tissue, the T1r dispersion at very low field strengths be related to the T1 dispersion of the same tissue at higher field strengths. However, both the T1r and T1 dispersion of several biological tissues have shown a weak dependence on field strength. This is vastly different from the quadratic frequency relationship expected for the interactions between magnetic dipoles in non-complex, homogeneous systems. Although simple power laws have been fitted accurately to the model of T1 dispersion in a variety of different tissues, it is not known whether a similar relationship can describe tissue T1r dispersion. Therefore, we measured and compared the ability of two such power laws, each with three fitting parameters, to characterize T1r dispersion in BSA solutions and patellar cartilage which were cross-linked. This was done over a range from 0.8 to 40 KHz. We project fitting T1r dispersion data to high field T1 measurements in order to determine whether our simple power law relationships exhibit limited dynamic range due to differences in the mechanism of relaxation corresponding to different field strengths. The results of our work have implications for current understanding of the relationship between T1r/ T1 and the mechanism of relaxation in the water protons of breast tissues.

Enhanced Protective Immunity by Recombinant Murine Interleukin-12 is Preceded by a Transient Suppression of Anti-Tumor Immunologic Responses

There is currently exploration into cytokine based strategies by which to induce an immunologic reaction against tumors. Such strategies are of particular interest for their potential to elicit a durable, effective response from the immune system without being excessively toxic. Among the cytokines tested, one of the most promising is interleukin 12 (IL-12). It has demonstrated consistent activity against a variety of murine tumors, be it in the form of a recombinant protein or as a cytokine secreted by tumor cells engineered for that purpose. The use of recombinant IL-12 (rIL-12) is particularly conducive to clinical application since it avoids the need for gene transfer. IL-12 by itself is effective against many tumors and, in cases where it is not, combining it with B7 co-stimulatory molecules or IL-2 has proven equally effective. The cytokine can exert effects on lymphoid and non-lymphoid cells directly or indirectly (an example of the latter is via induction of IFN-gamma); these in turn alter the host-tumor relationship favorably. Such effects include: the induction of Th1 differentiation and the anti-tumor response mediated by the cell; the activation of NK cells; the inhibition of tumor angiogenesis; the induction of nitric oxide production; and the up-regulation of MHC expression in the tumor cell. This pleiotropy of actions makes it difficult to isolate the specific mechanism(s) underlying the effectiveness of IL-12 against tumors.

Our studies of rmIL-12 and its anti-tumor effects have revealed that it can synergistically induce protective immunity against poorly immunogenic SCK mammary carcinoma cells, in conjunction with the expression of B7-1 co-stimulatory molecules in tumor cells. Although we established that $CD8^+$ T cells were essential to protection, we could not detect any cytolytic activity in the spleens of treated mice prior to re-challenging the SCK cells. It was our goal to determine the mechanism of rmIL-12 efficacy. Our studies primarily focused on the effect that rmIL-12 exerts on vaccination brought about by irradiated SCK tumor cells that secrete GM-CSF. Because of the nature of the vaccine, which induced measurable anti-tumor responses both *in vivo* and *in vitro,* we were able to evaluate the effects of superimposed rmIL-12.

Surprisingly, administering rmIL-12 ultimately ablated evidence of anti-tumor CTL activity in the spleen. It also attenuated, in direct correlation with the dosage, the secretion by splenocytes of tumor-specific cytokines. Such impaired responses were associated with a similar dose-dependent reduction in the ability of mice to reject a tumor cell challenge 14 days after vaccination. *In vitro* measurements of anti-tumor reactivity remained suppressed up to six weeks following vaccination. Additionally, splenocyte responses to Con A and IL-2 were suppressed 14 days after vaccination, but had returned to normal by one month after vaccination. We hypothesized that the suppressive effect of rmIL-12 seen at 14 days could have been due either to the impaired immunization or to the effector (rejection) response. To test this later possibility directly, we chose to determine protective immunity in rmIL-12 treated animals 28 days after vaccination, at a time when mitogenic responses have returned to normal. Vaccinated mice that received rmIL-12 were much better able to reject tumor cells than vaccinated mice that had not received rmIL-12 at this later time.

From these studies, we can conclude that rIL-12 is a promising adjuvant for a tumor cell vaccine; however, its ability to suppress immunologic responses temporarily suggests the need to establish sound guidelines for the proper dosage and scheduling of the medication. While in the clinic involved in our work, we will need to provide careful immunologic monitoring during various protocols of rIL-12 use in order to determine whether the issues raised here are significant in human cancer therapy. By doing so, our aim is to optimize the use of this compound as an immunologic adjuvant and as an anti-tumor agent.

The following is a list of trainees supported this year, including the period of their appointment and the names of their individual advisors:

Trainees	Period of Appointment	Advisors
Enn-Ling Chen	9/1/96 — 8/31/97	John S. Leigh, Ph.D. Gilles McKenna, MD/Ph.D.
Holly Kurzawa	6/1/96 — 5/31/98	William Lee, MD/Ph.D. Yvonne Paterson, Ph.D.
Donald Li	8/1/96 — 7/31/97	Barbara Fowble, MD John S. Leigh, Ph.D.
Jeff Souris	9/1/96 — 8/31/97	Britton Chance, Ph.D. Mitchell Schnall, MD/Ph.D.

Enn-Ling Chen

Enn-Ling Chen is a graduate student in the Structural Biology and Molecular Biophysics Graduate Group. Enn-Ling is at the dissertation level of her studies. The entirety of her training was devoted to developing and implementing experimental procedures for incorporation into her doctoral thesis, which she is currently writing and which she hopes to have completed by the end of the academic year. Gilles McKenna, MD, Ph.D. serves as Enn-Ling's clinical advisor. Dr. McKenna is chairman of the Department of Radiation Oncology and his primary interests include the identification of molecular and genetic markers in tumors that indicate resistance and/or sensitivity to radio waves. Enn-Ling's other advisor, John S. Leigh, Ph.D., is the Britton Chance professor of radiology and director of radiology research at the University of Pennsylvania. His considerable knowledge of the parameters involved in magnetic tissue imaging provides an excellent resource for Enn-Ling as technological issues present themselves throughout the course of her training work.

Holly Kurzawa

Holly Kurzawa was appointed as a program trainee on June 1, 1996. She is a student in the Cell and Molecular Biology Graduate Group. Her primary clinical advisor is William Lee, MD, Ph.D., who is an associate professor at the University of Pennsylvania with attending duties in the department of medicine. His particular expertise lies in the areas of tumor cell vaccines, their incorporation into therapeutic practice, and the regulation of gene expression. Holly has worked closely with him and with Yvonne Paterson, Ph.D., her scientific advisor. Dr. Paterson's specialty is in the regulation of the immune system, particularly biological and biophysical approaches to the regulation of T-cells. Holly attended the 1996 Cancer Vaccine Meeting in New York, as well as the Gordon Conference on Cancer in August of 1997, where she presented a poster. She regularly attends a seminar series within the Cell and Molecular Biology Group.

Donald Li

Donald Li is a graduate student in the Structural Biology and Molecular Biophysics Graduate Group. He completed his third year in the training program on July 31, 1997. His clinical advisor is Barbara Fowble, MD, a radiation oncologist who specializes in treating breast cancer in patients. In her capacity as clinician she is able to introduce Donald to human subjects for his studies; her prior clinical acquaintance with these people further enables him to tailor his research to individual patient histories. Donald presented his work at the Annual Retreat of the Department of Structural Biology and Molecular Biophysics. His other advisor is John S. Leigh, Ph.D., Britton Chance professor of radiology and director of radiology research at the University of Pennsylvania. Under his guidance, Donald has become proficient in programming techniques for use in the development of general imaging procedures. Donald has also been trained in clinical methods of tumor detection that involve the use of contrast agents.

Jeffrey S. Souris

Jeffrey Souris is a graduate student in the Structural Biology and Molecular Biophysics Graduate Group. Jeff completed his third year in the training program on August 31, 1997 and was re-appointed for a fourth year. During the year he has worked with his two advisors, Drs. Britton Chance and Mitchell Schnall. Dr. Schnall is both a skilled clinician and researcher who has actively pursued the development of NMR techniques for diagnosing breast and prostate cancer. Jeff has been trained in a technique, called Photon Diffusion Imaging, that is potentially useful in gathering imaging data from any number of tissues. This technique holds great promise as a new modality in the early detection of breast cancer, one that does not pose the hazards associated with x-rays. In working with his clinical advisor Jeff has learned about the nature and pathologic parameters of breast cancer, currently available diagnostic tools, and the strengths and weaknesses of these tools in detecting breast disease in its early stages.

CONCLUSIONS

We consider the process of education within the training program to be highly mutual. Trainees cull vast amounts of information about the pathology and treatment of breast cancer through discussion with their advisors and regular attendance at seminar series and conferences related to or directly dealing with the disease. In exchange, we expect trainees to disseminate their individual contributions to current knowledge via presentation of their work at conferences and conventions within the scientific community and within the larger community of persons concerned with or affected by the disease.

To be specific, we require that all trainees attend a monthly seminar series called FOCUS, which is hosted by the Group for Women's Health Research and deals with many issues facing today's breast cancer researchers. There are similar seminar series within the Department of Biochemistry and Biophysics and the Department of Cell and Molecular Biology which provide trainees with a solid grounding in the work being done in the broader fields of pathology and oncology. In addition, trainees have traveled to meetings and conferences all over the country to present their work and to elicit feedback from experts in their individual fields. Towards the end of reaching the more general scientific public, trainees have published papers and findings in widely-read scientific journals, newsletters, and brochures. These latter serve the double function of increasing awareness about the training program at the same time that they report on the work of the individual trainees.

The external advisor to our training program is Joann S. Ingwall, Ph.D. She is professor of medicine at Harvard Medical School. Dr. Ingwall's primary obligations to the program consist of offering advice and guidance to the director of the program. In addition, she reviews the progress of all present trainees and suggests possible alterations or improvements to the path of their research.

Our experience thus far with the program has been decidedly positive; we have found it to be an excellent mechanism by which to equip promising researchers with an enormous amount of clinical and technological knowledge relating to breast cancer detection and treatment. We have a strong desire to expand the program within our laboratory to accommodate yet more trainees and to expand the scope of our professional liaisons to include clinicians and research experts from an even greater geographic area.

We continue to search ardently for qualified minority and women candidates and to encourage their interest in the program. Half of our four current trainees are women. The program is promoted to minority candidates by a number of means. We send informational brochures to medical and engineering schools with large minority populations. We also contact persons at the University of Pennsylvania's medical school, biochemical graduate studies office, and engineering school who are qualified to refer interested candidates to us. Through these contacts, we ensure that the program is prominently advertised the minority outreach efforts undertaken by these schools. We keep our contacts informed of scientific workshops, seminars, and training sessions going on within our facility, stressing that interested minority candidates are encouraged to attend. Such events are excellent opportunities for the candidates to interact with the faculty and to be introduced to the specific work we do.

Having obtained the names of potentially eligible minority candidates, we invite them to submit their application to the program and to visit our facility to learn more about opportunities in breast cancer research and about the nature of the training program. In this way, we hope to provide as much information and encouragement as possible to minority candidates to aid them in their decision whether to apply.

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